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ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,913	ARENAS ET AL.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed, after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-15,29-35,37-43 and 62-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-15,29-35,37-43 and 62-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/01/01* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/16/04,3/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.D.O.

DETAILED ACTION

Receipt is acknowledged of an amended set of claims filed 5/20/2005. Claims 4, 16-28, 36 and 44-61 have been canceled, and claims 62-69 have been added. Claims 1-3, 5-15, 29-35, 37-43, and 62-69 are currently pending.

Information Disclosure Statement

Receipt is acknowledged of information disclosure statements filed 11/16/2004 and 3/31/2005.

Drawings

The drawings are objected to because the capitalization of the panel letters does not match those in the Brief Descriptions of the Drawings (Specification, pages 26-28). For example, the Brief Description of Figure 1 identifies the individual panels with capital letters A-C, while in the drawings themselves, the panels are identified with lower case letters a-c, as are the panels in Figure 2. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary

to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-31, 37-43 and 62-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants claim methods for screening for factor(s) and receptor(s) for factor(s) which are obtained from Type1 astrocytes of the mesencephalon which induce a dopaminergic fate in neural stem or progenitor cells. The invention is also drawn to screening for substance(s) which modulate the ability of said Type 1 astrocytes to induce a neuronal cell fate,

The rejection of claims 29-31 and 37-43 for lack of written description are maintained for reasons of record in the previous office action (mailed 5/11/2004) and for reasons outlined below.

Applicants argue that the receptor screening method of claims 29 and 30 is described in the present specification at page 23, and the factor screening method of claims 31 and 37-43 is described in the present specification at pages 20-23.

Applicant's arguments filed 11/16/2004 have been fully considered but they are not persuasive. The specification describes methods of screening for factor or factors to induce a dopaminergic fate in neural stem or progenitor cells expressing Nurr1 above normal levels in which the screening methods include comparison of Type 1 astrocytes of the ventral mesencephalon with astrocytes from other neural locations (page 21-22). The specification also teaches that the screening method may involve purifying or isolating substance(s) from a mixture and any factor(s) identified by one of the screening methods may be isolated and further investigated. The specification also describes methods of screening for a substance which modulates the ability of Type 1 astrocytes of the ventral mesencephalon (or of a factor(s) identified by a screening method provided by the invention) to induce a dopaminergic fate in neural stem or progenitor cells expressing Nurr1 above normal levels.

The disclosure does not provide adequate written description of any, or even one of the said factors which might be obtained from Type 1 astrocytes of the ventral mesencephalon. The specification provides no examples to suggest that the Applicants have identified any factors from Type 1 astrocytes which would induce a dopaminergic

fate in other cell types. No structural characteristics for the factor or factors that mediate the observed dopaminergic development have been provided beyond the observation that at least one such factor appears to be secretable. Absent any details about the factors which may be obtained from Type 1 astrocytes which have said effect, any type of a myriad of factors may have the ability to effect neural stem or progenitor cells, amounting to an incredibly large genus of factors.

The instant claims are drawn to a method of screening for and identifying receptors which bind members of the incredibly large genus of Type 1 astrocyte factors. Given that the factors can be of ANY type obtainable from astrocytes, then the receptors for those factors must consist of, at least, an equally large group. Therefore, it cannot be concluded that applicants had in their possession the relatively isolated factor or factors required to practice the claimed invention in the broadly recited genus of methods embraced by the rejected claims. There is no basis in the instant specification for the skilled artisan to envision any specific factor or combination of factors obtainable from Type 1 astrocytes that will satisfy the functional limitations of the claims.

In addition, the claims are drawn to a method using identified receptors for Type 1 astrocyte factors in order to screen for said factors obtained from Type 1 astrocytes. These claims include downstream uses of receptors found in a previous screening method to screen for factors which bind to the receptors. These claims are termed "reach through claims" and rejection is proper on the grounds that the applicants do not possess the factor (s) of type 1 astrocytes or the receptor or receptors of the claimed

invention and therefore have no *a priori* knowledge of what factors might be identified by the screening method.

Applicants were able to obtain a secreted factor in an embodiment of the invention only (i.e. the presence of the Type 1 astrocytes). Applicants have not shown the means for obtaining the factor or factors responsible for the observed inductive effect on neuronal stem or progenitor cells. Any assertion of the fact that at least one of the factors that mediates the induction of dopaminergic cell fate on the neuronal stem or progenitor cells is secretable does not provide a framework for the skilled artisan to reliably envision which of the many factors, or combinations of factors, that are secretable by Type 1 astrocytes are responsible for the observed functional effects on neuronal precursor cells. The disclosure of the invention does not show that applicants could accurately predict at the time of filing which of the many factors, or combination of factors, secretable from Type 1 astrocytes will necessarily meet the functional limitations of the claims.

Given that the claims encompass a potentially broad genus of dopaminergic-inducing factors or combination of factors, it is necessary for applicants or the prior art to provide some description of the structural/functional characteristics of such factors in order to demonstrate possession of the broadly claimed genus of methods using such factors. For the reasons outlined above, there was no basis provided by the specification and prior art at the time of filing for the skilled artisan to envision even one such factor that would meet the functional requirements of the claimed methods, much less the broadly claimed genus of such factors or combinations of factors. Therefore,

the skilled artisan would reasonably have concluded applicants were not in possession of the claimed methods.

Claims 62-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **These are new rejections necessitated by amendment filed 5/20/05.** Applicants claim a method of inducing a dopaminergic neuronal cell fate in a neural stem or progenitor cell expressing Nurr1 levels above basal levels in an *in vitro* co culture with Type 1 astrocytes from the ventral mesencephalon by contacting the cell with a substance which modulates the ability of the astrocytes to induce the dopaminergic cell fate and a method of treatment of Parkinson's disease with said substances which have been screened for their ability to modulate astrocytes and subsequently isolated and purified.

The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, such as structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention. In the instant case, the specification does not disclose any structure for a

substance or substances that might have the ability to affect Type 1 astrocyte activity, nor does it disclose any homologue or derivative of such a substance. The specification has provided no disclosure on any possible functional motifs of these substance(s) which the skilled artisan might expect to be shared by a functional family of these substances.

Instant claims regarding treatment of Parkinson's disease with a substance which was identified in a screening method via modulation of the ability of a Type 1 astrocyte to induce neuronal cell differentiation are likewise not described because they make use of substances which have not been shown to be identified, much less isolated and purified. The specification does not disclose specific treatment methods on how the substance would be implanted into the brain, or any effort to address potential side effects of this treatment. It does not teach effective dosage amounts or dosage frequency. According to these facts, one of skill in the art would conclude the applicant was not in possession of the claimed substance or method of use of the substances at the time the invention was made.

Claims 13-15, 29-35, 37-43 and 66-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants claim a method for screening for receptor(s) for factor(s) which are obtainable from Type 1 astrocytes of the mesencephalon which

induce a dopaminergic cell fate in neural stem cells which are expressing Nurr1 above basal levels and subsequently cloning the gene(s) for said receptor(s) for use in methods to screen for factor(s) which induce a dopaminergic cell fate.

The rejection of claims 29-35 and 37-40 under 35 U.S.C. 112, first paragraph for failing to comply with the total enablement requirement is being maintained for reasons of record in the previous office action and for reasons outlined below. **New claim 69 is now included in this rejection necessitated by amendment.** Claim 69 includes the method of claim 32 of screening for factor(s) inducing a dopaminergic cell fate comprising binding molecules from Type 1 astrocytes to progenitor cells and identifying said molecules as cell fate-inducing factors by the occurrence of their binding to the stem cell and further comparing expression of molecules by said astrocytes to neural cells unable to induce neuronal cell fate.

Applicants argue they have provided substantial guidance as to how to perform the claimed method and cite the specification which discloses at page 23, lines 7-17 that cells expressing above basal levels of Nurr1 can be compared to normal cells by "any known method for analyzing a phenotypic difference between cells and may be at the DNA, mRNA, CDNA, or polypeptide level." The specification further teaches at page 21, lines 26-33 that the interaction between, the factor and the receptor, "may be determined by any number of techniques in the art" including "labeling either one with a detectable label and bringing it into contact with the other which may have been immobilized on a solid support, e.g. by using an antibody bound to a solid support."

Applicants submit that the above teachings are sufficient, in view of the techniques widely known and used by skilled artisans at the time of the invention, to enable one skilled in the art to perform the instantly claimed methods. Applicants cite that art at the time that the invention was made, taught how to identify receptors for human papillomavirus (See Evander et al, of record) and identification of the binding partner of a low-density lipoprotein receptor related protein (See Ranganathan et al, of record). Applicants submit that a skilled artisan, in view of prior art teachings and the guidance of the instant specification, could arrive at various means to identify the receptor of the factor secreted by Type 1 astrocytes.

Applicant's arguments filed 11/16/2004 have been fully considered but they are not persuasive. Examiner acknowledges that multiple methods do exist to identify proteins and their binding partners. There is no doubt that a multitude of proteins and receptors could be pulled out of a screen of neural stem or progenitor cells expressing Nurr1 above basal levels and Type 1 astrocytes. However, instant claims 29-30 and 37-43 are directed to screening for specific receptor(s) for a factor(s) that, either alone or in combination, induce a dopaminergic fate in a neural stem or progenitor cell expressing Nurr1 above basal levels. Claims 31-36 are directed to methods of screening for factors that, either alone or in combination, induce a dopaminergic fate in neural stem or progenitor cells expressing Nurr1 above basal levels. As such the claims encompass embodiments where the factors are actually obtained in some form or identified.

Applicant has not demonstrated or described a screening method in which the specific factor(s) and their respective receptors(s) can not only be found, but also

distinguished from any and all other factor(s) and receptor(s) which might be found in such a broad screening assay, as having the ability to induce dopaminergic fate in a neural stem or progenitor cell expressing Nurr1 above basal levels. Given the limitations recited in the claims, the invention requires some knowledge of the identity of receptor(s) for the factor(s) that are involved in the induction of dopaminergic cell fate. The method of claim 69 has no guidance as to what steps will be used to compare the expression of molecules from astrocytes with expression of molecules from neural cells that are unable to induce said neuronal cell fate. No information on how the differentially expressed molecules that actually induce said cell fate will be distinguished from differentially expressed molecules of Type 1 astrocytes which do not have the ability to induce a dopaminergic cell fate.

Given the combination of factors outlined above, particularly with regard to applicants' own inability to identify or further characterize the factor(s) responsible for the observed induction of a dopaminergic cell fate for neuronal stem or progenitor cells in cocultures of such neuronal precursors and Type 1 astrocytes, it would have required undue, unpredictable experimentation to identify such factors and/or their receptors using the recited methods.

Claims 13-15, 41-43 and 66-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention. **Rejection of claims 41-43 are new rejections. Rejection of claims 66-68 is necessitated by amendment.** Applicants claim *in vivo* methods of treating Parkinson's disease by administering a composition into the brain of an individual wherein the composition is comprised of a neural stem cell or progenitor cell expressing Nurr1 above basal levels and a factor(s) able to a induce a dopaminergic cell fate (claims 41-43). Applicants claim *in vivo* methods of treating Parkinson's disease by administering a composition into the brain of an individual wherein the composition is comprised of a substance that can modulate the ability of a Type 1 astrocyte, or a molecule(s) of the astrocyte to induce a dopaminergic fate in neural stem or progenitor cells

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte* Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re* Wands, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

1) Nature of the invention. The claims are directed to *in vivo* embodiments of methods of inducing a dopaminergic neuronal cell fate for neural stem cells or neural progenitor cells where the neural stem cell or progenitor cell expresses Nurr1 above basal levels. The specification teaches that the invention includes embodiments where

cells overexpressing Nurr1 are induced to a neural cell fate *in vivo* (e.g. by recombinant means and/or treatment with factors) and where the induced cells are co-administered with one or more factors that mediate the dopaminergic cell fate that are secreted by Type 1 astrocytes obtained from the ventral mesencephalon. As the specification discloses recombinant means for inducing the dopaminergic cell fate on the neuronal precursor cells, claims 41-43 read explicitly on *ex vivo* methods of therapy. Claims 66-69 are drawn to implantation in the brain a substance(s) as yet unidentified or characterized, except for the criteria that the substance(s) should modulate Type 1 astrocyte-induced differentiation of neural stem cells

The claims read on treatment of a neurological disorder of the brain featuring the delivery of Nurr1-overexpressing neural stem cells to the appropriate portion of the brain in a therapeutic manner, for induction of such a cell fate on neuronal progenitor cells *in situ* and/or by providing such potential dopaminergic cells *ex vivo*. The claims also read on treatment of a neurological disorder by implantation of a substance identified as a modulator of astrocyte activity. Therefore, the methods claimed are exceedingly complex, involving the manipulation of cell fate in a progenitor population of cells including embodiments where the manipulation is via various factors or substances, for therapeutic effect in the brains of individuals, including humans, suffering from neurological disorders such as Parkinson's disease.

2) Scope of the invention The broadest interpretation of the claims reads on a method of co-administering progenitor or stem cells with some factor(s) from Type 1 astrocytes identified as having the effect of inducing dopaminergic fate on the stem

cells. It also reads on administration to the brain of an individual a substance that modulates the ability of Type 1 astrocytes to induce stem cell to a neural cell fate. The substance(s) is only described as being able to modulate the ability of Type 1 astrocytes to induce neural cell fate. As written, a substance could include a small molecule drug or a gene for a growth factor in an adenoviral vector and include embodiments where the methods claimed is a method of gene therapy. Therefore, the methods claimed are exceedingly complex, involving the manipulation of cell fate in a progenitor population of cells including embodiments where the manipulation is treatment with a substance, for therapeutic effect in the brains of individuals, including humans, suffering from Parkinson's disease.

3) Unpredictability of the art. Information available at the time the invention was made suggests multiple problems associated with the therapeutic implantation of stem or progenitor cells into the brain for treatment of neurological disorders (see Gerlach et al. J. Neurol. 2002. Vol. 249. Supplement pp. III33-III/35). Gerlach et al teaches that fetal neurons have been implanted in ~300 Parkinson's patients, some of whom have shown improvement in their conditions. However, Gerlach et al cite that multiple problems are related to this treatment including variations in therapeutic effect, side effects and the difficulty in using fetal or stem cell tissue (see pp. III/34, column 1, paragraph 3, for example). The unpredictability of this treatment lies in the unregulated proliferative potential of neural stem cells. Clinical evidence has shown that uncontrolled neural progenitor cell growth and differentiation in the brain of a Parkinson's disease patient resulted in death. In light of this, Garlach et al suggest therapeutic implantation

of cells differentiated *in vitro* prior to implantation, but also cite the need for elimination of the possibility of uncontrolled proliferation and long term preliminary studies in animals prior to widespread administration of neural progenitor cells in human patients (See pp III/34, column 2, paragraph 3, in particular). An analysis of the prior art as of the effective filing date of the present application shows a complete lack of documented success for any treatment based on gene therapy.

In a review on the current status of gene therapy, both Verma et al (Nature (1997) 389:239-242) and Palù et al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved (e.g. Verna et al, p. 239, paragraph 1; Palù et al p. 1, Abstract). The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. While the current art indicates the potential of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique (see Verma et al, p. 242, col. 2-3; Palù et al, pp. 10-11; Luo et al , p. 33, col. 1, paragraph 1).

Hsich et al teach in a post-filing review of the neurological field (Human Gene Therapy, Vol. 13, pages 579-604, March 2002, see the entire review for example) that gene therapy treatment of such disorders must include recognition of the inherent toxicity and immunogenicity of typical gene therapy vectors and accompanying damage to neurons due to inflammatory responses and edema, induction of self-antigen responses, injection injuries and the resulting need for long-term expression of transgenes in vivo, etc. (see page 579, introductory paragraph, for example) such as

might be necessary for maintenance of Nurr1 expression above basal levels in the stem or progenitor cells. Hsich et al teach that although even low levels of expression of a transgene may be therapeutic, unintended consequences can readily occur if overexpression in the cells has additional effects on the surrounding cells (see page 583, first paragraph for example). Hsich et al teach that several factors need to be addressed with regard to the treatment of neurodegenerative diseases such as Parkinson's disease. These include careful assessment of potential toxicity caused by the vector and transplanted cells or by enhanced synthesis of dopa/dopamine, and of abnormal sprouting or apoptosis caused by growth factors. Hsich et al further teach that, because the basis of intrinsic toxicity underlying Parkinson's disease in humans is not addressed in the experimental animal models used for gene therapy, the data obtained in such animal model systems may not prove predictive of effects in humans (see page 594, column 2, paragraph 2).

4) State of the art. Stem cell therapy for the treatment of neurological diseases such as Parkinson's disease appears to have great potential. However the art in the field of stem cell therapy for neurological disorders in poorly developed. Garlach et al stress the need long term preliminary studies in animals prior to widespread administration of neural progenitor cells in human patients (See pp III/34, column 2, paragraph 3, in particular). In the instant case, the inventions involve implantation of compositions comprising not only neural stem cells but also unidentified factors, or substances which modulate progenitor cell fate and have a low rate of predictability of success given the high number of unknown and uncharacterized factors. Given that the applicant provides no *in*

vivo data which might be predictive of results, it must be considered that the skilled artisan would have had to have practiced trial and error experimentation in order to practice the claimed invention.

5) Level of skill in the art The relative skill required in the art of treating neurological disorders of the brain is very high. This high level of skill required to practice the claimed methods is highlighted in the embodiments that feature recombinant methodologies for the overexpression of Nurr1 in the neuronal stem or progenitor cells, whether *in situ* within the brain or *ex vivo*, where a multiple technical difficulties must be overcome (e.g. regulating overexpression of Nurr1 at appropriate levels, delivery of nucleic acids to the appropriate host cell population, delivery of sufficient number of dopaminergic cells to the appropriate place in the brain, long-term maintenance of transplanted cells in the brain produce a therapeutic effect, for example). However the level of skill in actually practicing the claimed inventions for inducing neural stem cell to a dopaminergic cell fate with factors from astrocyte or substances that modulate astrocytes is very low because they have not reduced the inventions to practice.

6) Working examples Applicant present no working examples of successful treatment or method to implant a composition comprised of factors identified and isolated from astrocytes as able to induce a dopaminergic cell fate in neural stem cells, in combination with the neural stem cells. Applicant presents no working examples of efficacious *in vivo* treatment of individuals with Parkinson's disease by implantation of substances identified for their ability to modulate the ability of Type 1 astrocytes to induce neural stem cells to a dopaminergic cell fate.

7) Amount of guidance presented by applicant. Applicant presents no guidance on how a composition comprised of factors(s) and neural progenitor cells expressing Nurr1 above normal levels, or a composition comprising a substance that modulates astrocytes would be implanted in individuals with a neurological disorder such as Parkinson's disease. Applicants have not demonstrated success in identifying such a substance, much less isolating and purifying the substance or substances. In addition, no structural or functional information has been provided about said substances. There is no guidance as to what amount of composition implanted would be therapeutic, what percentage of the progenitor cell must be expressing Nurr1 above normal levels, or whether there is a threshold of Nurr1 expression over basal levels which must be achieved before optimal induction of cell fate via astrocyte factors occurs. There is no guidance on what side effects may occur as a result of the treatment or as a result of the implantation procedure. Some neurological disorders are degenerative and long term, but applicant does not suggest whether multiple treatments may be necessary or efficacious. Applicant presents no guidance on how the skilled artisan would overcome the art recognized problems stated above associated with gene therapy or stem cell therapy procedures.

Given the analysis of the above factors which the Courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have needed to have practiced undue and excessive experimentation, with little guidance from applicants in order to attempt to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29, 30 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 29, 30 and 37 is being maintained for reasons of record in the previous office action and for reasons stated below. Applicant traverses the rejection of claim 29 on the grounds that there is a clear nexus between the stated outcome of the claimed method and the actual method steps recited because identification of the receptor(s) is accomplished by comparison of the cells which do or do not express Nurr1 above basal levels. The method further includes isolated and/ or purifying and/or cloning the gene(s) encoding the receptor(s) in claim 30. Applicants argue that there is an inherent scope of difference in the respective terms of isolating and purifying.

Applicants' arguments have been fully considered but they are not persuasive. The method of claim 29 remains unclear, although the factors are now obtained from astrocytes, they are not included in a step of the method which, as currently written include only comparison of neural stem cells with or without expression of nurr1 above basal levels. One of skill in the art would not be able to determine from the claimed method how to screen for a factor-specific receptor by simply comparing cells with and without elevated expression of Nurr1. If the applicant intends that factors which have

been obtained from Type1 astrocytes are to be contacted with neural stem or progenitor cells, so that the factor(s) would bind to factor-specific receptors present on cells with increased Nurr1 expression and not bind to cells with endogenous Nurr1 expression in such a way that the cells are easily distinguishable from one another either visually, behaviorally or biochemically and thus identify the receptor(s), applicant could amend the claims to include additional steps, and especially including a step which utilizes the factor(s) in the screening method.

The limitations of the phrase "isolating and/ or purifying" remain unclear in claims 30 and 37. The skilled artisan cannot determine from the claims as written what methods to use in order to isolate, but not purify the receptors or what further step would be involved in purification of an isolated protein. Claim 37 does not specify what degree of either isolation and purification would be necessary for said method, or if crude isolation of the factors only would be sufficient for the method as claimed. The indefiniteness of the claims stems from the phrase "and/or." It would be remedial to amend the claim to further briefly describe steps in which the receptors are isolated and purified, and also steps in which the receptor(s) are only isolated, or in which the receptors are only purified.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 5-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bowen et al (U.S. Patent No. 6,284,539), in view of Takeshima et al (Neuroscience 1994. 60(3):809-823). **This is a new rejection necessitated by amendment.** The applicants claim a method of producing a dopaminergic neuronal fate in a neural stem cell by expressing Nurr1 above basal levels, and co-culturing the cell *in vitro* with a Type 1 astrocyte of the ventral mesencephalon, thereby contacting the cell with factor(s) secreted from the astrocyte. The cell can be contacted with other agents such as growth factors.

Bowen et al teaches a method of directing cell fate for precursor cells of the central nervous system by the introduction and endogenous expression of a gene coding for the nuclear receptor Nurr1 in order to direct neuronal precursors to a dopaminergic cell fate which is verified by expression of tyrosine hydroxylase (See abstract, and examples 1 and 2, in particular) which reads on inducing a neuronal cell fate in a neural stem cell by expressing Nurr1. Bowen et al teach overnight culture of the stem cells with bFGF prior to transfection which reads on the method comprising steps in which the stem cell is pretreated with bFGF (see column 10, Transfection, lines 15-17, in particular). In the background of the invention, Bowen discloses that co-culturing dopaminergic neurons with striatal astrocytes or with conditioned media from striatal astrocytes has been shown to increase the survival of the neurons (See column 3, lines 11-25, in particular).

Bowen et al do not disclose that neuronal stem cells are co-cultured with Type 1 astrocytes of the ventral mesencephalon in order to induce the development of dopaminergic neurons.

Takeshima et al teach that cells from the mesencephalon of embryonic rats were plated on a confluent monolayer of ventral mesencephalic astrocytes and showed an increase in dopaminergic cell number, and also exhibited changes consistent with neuronal cell development (See Abstract, page 816, column 1, paragraph 2 bridging to column 2, in particular), which read on co-culturing neural progenitor cells with Type 1 astrocytes of the mesencephalon and inducing a dopaminergic neuronal fate. Takeshima suggests that the Type 1 astrocytes may produce a factor that acts selectively on the dopaminergic neural phenotype (see page 819, paragraph 1, for example).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Bowen et al to include co-cultures of ventral mesencephalic astrocytes to support the growth and increase the survival of dopaminergic neurons with increased levels of Nurr1 because Bowen et al discloses increased survival of dopaminergic neurons when in co-culture with astrocytes. Takeshima et al teach using a culture of Type 1 astrocytes of the mesencephalon to support the growth of developing dopaminergic neurons derived from embryonic rat brains. The motivation to do so is the expected benefit as suggested by Bowen et al and actually exemplified by Takeshima of being able to produce a viable culture of dopaminergic neurons. There is reasonable

expectation of success in using ventral mesencephalic astrocytes to support the development of neurons since this has worked previously in the cited techniques.

Conclusion

Rejections of claims in the previous action which have not been mention herein are withdrawn. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-8300.

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DAVID GUZO
PRIMARY EXAMINER

Laura McGillem, PhD
7/25/2005